REMARKS

Applicants respectfully request reconsideration. Claims 42-52 and 56-78 were previously pending in this application. Claim 60 has been amended to a correct typographical error. No claims have been canceled or added. As a result, claims 42-52 and 56-78 are still pending for examination with claims 42 and 71 being independent claims. No new matter has been added.

Rejection Under 35 U.S.C. 112

Claim 60 has been objected to because of a typographical error. Applicants have amended claim 60 as suggested by the Examiner to insert the word "wherein". It is believed that the amendment is sufficient to overcome the rejection.

Claims 42-53 and 56-78 have been rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. Specifically, the Examiner has stated that "the specification provides insufficient guidance and objective evidence that such stabilized CpG immunostimulatory oligonucleotide would predictably treat cancer. The specification provides no guidance on the administration of the claimed oligonucleotide in vivo." (Office Action, page 4, second paragraph.) The Examiner has performed a Wands analysis.

Unpredictably of the Art and State of the Prior Art

The Examiner has cited Agrawal et al. (Trends in Mol. Med., 2002; 8: 114-121) for the teaching that cytokine induction in vivo depends on the sequences flanking the CpG dinucleotide, as well as the dose, the route of administration and the host animal species.

Agrawal is a review article summarizing numerous studies performed on CpG oligonucleotides and their effects on immune stimulation and potential use as therapeutics. Agrawal has described the therapeutic potential and utility of CpG DNA in human systems, including the use for treating cancer. A significant amount of discussion in Agrawal is directed to the production of second-generation immunostimulatory DNA that do not include CpG motifs. Although Agrawal recognizes that production of specific cytokines can be optimized by using specific CpG motifs with flanking sequences as well as dose and route of administration, Agrawal does not suggest that CpG

DNA is not useful therapeutically. The sections highlighted by the Examiner simply refer to optimization of the molecules. Demonstration that molecules can be optimized is not evidence that the invention as a whole is unpredictable. On page 116 Agrawal describes CpG in clinical trials and states that "Significant progress has been made in understanding the immunological and pharmacological affects of the first-generation CpG DNA molecules." (Second column, third paragraph.) Agrawal concludes by stating that "it is evident that CpG DNA is a powerful tool to modulate the immune system and can be exploited to treat a wide variety of diseases quite economically. Studies on the medicinal chemistry of CpG DNA have just begun and the preliminary results indicate several possible ways of further fine-tuning the immunomodulatory affects of first-generation CpG DNA by introducing site-specific chemical modifications." (Page 199, 2nd column 2nd paragraph).

On pages 8-9 of the Office Action the Examiner addresses Applicants' prior arguments with respect to Agrawal. According to the Examiner Agrawal et al. suggests undue experimentation would be needed for treatment methods using CpG containing oligonucleotides because although Agrawal describes significant progress, "only limited data are available on optimized CpG DNA agents in human clinical trials." The fact that limited data is available on optimized CpG DNA agents does not support the unpredictability of the invention or demonstrate that the invention would require undue experimentation. The claimed invention does not require the use of "optimized CpG DNA agents." Additionally, the fact that only limited data is available in human clinical trials does not suggest the invention would not work.

The Examiner also points to the teaching in Agrawal et al. that the pattern of cytokines in vivo depends on the sequences flanking the CpG dinucleotide "as well as the dose and the route of administration which are not yet known." (Page 8-9). Although Agrawal teaches the first part of the quoted sentence, Applicants could not identify where Agrawal states that the dose and route of administration are not yet known. Agrawal describes preliminary data from early stage clinical trials in the treatment of cancer (lymphoma, melanoma and basal cell carcinoma). If the compound is being administered to human patients in a clinical trial, at least preliminary therapeutically acceptable doses and routes of administration have been identified. Additionally, the last sentence

of the quoted paragraph explicitly states and approximate dose, i.e., that "CpG DNA elicit affects at $\mu g\ kg^{-1}$ doses." (Page 116, 2nd column, last sentence).

Finally, the Examiner concludes that because Agrawal et al. suggests that medicinal chemistry of CpG DNA has just begun and needs further fine-tuning, that this is an indication that at the time of filing of the instant application the claims were not enabled. Applicants disagree. At the time of the filing of the patent application, Applicants described a class of molecules useful for the treatment of cancer. Applicants fundamental invention is based at least in part on the discovery that the immune system detects bacterial DNA by the presence of unmethylated nucleotides, which can be present in a wide variety of base contexts. The applicant was the first to recognize that these immune activating effects of bacterial DNA could be reproduced using synthetic oligonucleotides containing unmethylated CpG. The fact that an author suggests that the medicinal chemistry of this class of molecules needs further fine-tuning at a later date does not indicate that the claimed invention lacks enablement. Even after drugs are used successfully in humans, researchers continue to do research and fine-tune various aspects of the drug. Optimization or preferential selection of species at a later point in time does not render the use of a genus of compounds unpredictable at an earlier time point.

The Examiner has also reiterated the unpredictability of the treatment of cancer as pointed out by Peterson et al., Schuh et al., Bibb et al. and Saijo et al. As Applicants previously argued in response to the first Office Action none of the Peterson et al., Schuh et al., Bibb et al. and Saijo et al. references describe the use of CpG oligonucleotides. Each of the references was cited to establish that pre-clinical work is not always predictive of clinical success. However, the law is well established that a clinical trial is not required for enablement. It is not proper for the Examiner to require clinical data to support the enablement of the invention. Although other therapeutic agents which had shown activity in pre-clinical models may have had minimal clinical activity as described in these references, this is not true with CpG oligonucleotides. As shown in the specification, Applicants generated pre-clinical data on CpG oligonucleotides that demonstrated activity consistent with the treatment of cancer. Currently there are a number of clinical trials being conducted with CpG oligonucleotides, including trials for the treatment of cancer with CpG oligonucleotides. As taught by Krieg et al. (Nat. Revs. 2006 v. 5 p. 471 (attached as Exhibit 1))

"encouraging evidence for the capacity of TLR9 activation to induce a TH1-like cytokine response in human cancer patients has been reported recently in studies in dendritic cells isolated from primary human tumours[100] and in lymphoma patients treated with a CpG ODN alone or together with an antitumour antibody." (Page 477, second column, last paragraph). In Table 2 on page 478 of Krieg, the human clinical trials being conducted or completed as of 1996 are listed. The clinical trials for cancer include a phase I monotherapy, a phase II vaccine therapy, and a phase I, II and III combination therapy. Additionally, a 2007 review article, Krieg, J. Clin Invest. 117, p. 1184, 2007 (attached as Exhibit 2), describes a summary of TLR9 agonists in cancer therapy. Table 2 lists published oncology clinical trials with TLR9 agonists and Table 3 lists ongoing oncology clinical trials with TLR9 agonists. Thus, the fact that several references teach that completely unrelated drugs showing preclinical activity but minimal clinical activity is not relevant to the predictability of CpG oligonucleotides which are already demonstrating promise in clinical trials.

Working Examples and Guidance in the Specification

The Examiner has stated that the specification has no working examples indicating that CpG oligonucleotides can be useful for treating any kind of cancer. On pages 9-11, the Examiner states that the data presented in the specification is not sufficient to establish that the claimed oligonucleotides will be useful for the treatment of cancer. The Examiner invites the Applicants to identify places in the specification providing a correlation between the scope of the claims in the specification. The Examiner further cites Zips et al. (New Anti-cancer Agents: In Vitro and In Vivo Evaluation, 2005, In vivo, 19:1-7) for the teaching that in vitro data is not sufficient to establish tumor response to drugs.

In the specification, Applicants have taught that oligonucleotides containing an unmethylated CpG dinucleotide produced an immune response that is consistent with the treatment of cancer. Applicants have taught routes of administration. Applicants have provided numerous examples of oligonucleotides falling within the genus of molecules. Significant amounts of data demonstrating the specific effects of CpG oligonucleotides are provided in the specification. The data confirms the specificity of the claimed motif by showing oligonucleotides having an unmethylated CpG dinucleotide are capable of inducing an immune response whereas

oligonucleotides having the same sequence of nucleotides but a methylated C instead of an unmethylated C lose activity.

One distinction between Applicants invention and other systems for testing drugs for the treatment of cancer is that the CpG oligonucleotides of the invention are acting through stimulation of an immune response in a host. That immune response in the host then attacks the cancer and produces the therapeutic result. Many other anti-cancer drugs have affects on localized systems such as the cancer cells themselves or the vasculature associated with the tumor. These types of drugs require targeting and therapeutic activity at localized regions. Unlike these drugs, CpG oligonucleotides when exposed to immune cells enhance the body's reaction to the tumor.

In the specification Applicants have demonstrated that oligonucleotides containing an unmethylated CpG are effective at stimulating B-cell proliferation (Table 1), IgM secretion (page 26), IL-6 production (pages 26-27, Table 3, pages 28-30, and Table 4), induction of TNF-α (page 30 and Tables 5-7), induction of IL-12 (pages 30-32 and Tables 5-6), induction of IFN-γ (pages 30-32 and Tables 5-6), induction of GM-CSF (pages 30-33 and Tables 5-7), and induction of NK Cell Stimulatory Activity (pages 36-44 and Tables 8-11). The description and the data found in the specification establish a pattern of immune stimulation which is consistent with the treatment of cancer. The data is sufficient to establish to one of skill in the art that this class of drugs is sufficient to promote an immune response which helps the host body's immune system attack the cancer.

Quantity of Experimentation

The Examiner also addresses the quantity of experimentation. According to the Examiner, "The amount of additional experimentation is deemed to be undue because in order to practice the claimed invention with a reasonable expectation of success, one of skill in the art would have to show evidence overcoming art recognized problems that the broadly claimed CpG-containing oligonucleotides would not work for treating or preventing any cancer." (Office Action page 7). Applicants disagree. Applicants have taught in the specification that a class of compounds is useful for treating cancer. Exemplary dosages and routes of administration are provided. The class of compounds includes oligonucleotides having a CpG motif. Methods are known in the art for

synthesizing oligonucleotides containing a CpG motif. The oligonucleotides can be purchased from numerous commercial sources. The oligonucleotide once synthesized could be administered to a subject having cancer, as is currently being performed in on-going human clinical trials. It is unclear to Applicants why the experimentation required to perform the method would be considered to be undue. One of skill in the art would simply need to follow the guidance provided in the specification using a class of molecules which is commercially available or easily synthesized.

Accordingly, withdrawal of the rejection of claims 42-53 and 56-78 under 35 U.S.C. §112 is respectfully requested.

CONCLUSION

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

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Respectfully submitted,

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